

Dae-Kee Kim*, Hun-Taek Kim, Jinsoo Lim, Jongsik Gam,
Young-Woo Kim and Key H. Kim

Life Science Research Center, Sunkyong Industries, 600 Jungja-Dong, Changan-Ku, Suwon-Si,
Kyungki-Do 440-745, Korea

Young Oh Shin

Center for AIDS Research, National Institute of Health, 5 Nokbun-Dong, Eunpyung-Ku, Seoul 122-020, Korea
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**This paper is dedicated to Professor Nicholas Alexandrou,
Aristotelian University of Thessaloniki on the occasion of his death**

The 1,5-dialkyl-6-(arylselenenyl)uracils **10a-h** and -2-thiouracils **10i-p** have been synthesized as potential anti-HIV-1 agents. Cyclization of *N*-alkyl-*N'*-[3,3-di(methylthio)-2-alkylacryloyl]ureas **6a-d** and -thioureas **6e-h** in acetic acid either containing a catalytic amount of methanesulfonic acid at 80° or containing 1 equivalent of methanesulfonic acid at room temperature afforded 1,5-dialkyl-6-(methylthio)uracils **7a-d** in 84-96% yields and 1,5-dialkyl-5,6-dihydro-6,6-di(methylthio)-2-thiouracils **11a-d** in 88-99% yields, respectively. Oxidation of **7a-d** and **11a-d** with either 3-chloroperoxybenzoic acid in benzene or aqueous sodium periodate solution in methanol gave 1,5-dialkyl-6-(methylsulfonyl)uracils **8a-d** in 88-98% yields and 1,5-dialkyl-6-(methylsulfinyl)-2-thiouracils **12a-d** in 57-73% yields, respectively, which were subsequently treated with arylselenol **9a-b** in ethanolic sodium hydroxide solution to afford **10a-p** in 60-99% yields. Of these compounds, 6-[(3,5-dimethylphenyl)selenenyl]-5-isopropyl-1-(3-phenylpropyl)uracil (**10h**) inhibited HIV-1 replication in MT-4 cells at a 50% effective concentration (EC₅₀) of 0.0006 μM with a selective index of 44833, which is 7.7-fold more potent than AZT.

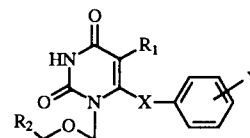
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Human immunodeficiency virus type 1 (HIV-1) is the causative agent of acquired immunodeficiency syndrome (AIDS), which is one of the world's most serious health problems, with current protocols being inadequate for either prevention or successful long-term treatment [1]. The reverse transcriptase (RT) encoded by HIV-1 catalyzes the conversion of the viral genomic RNA into proviral DNA [1]. Since RT is an essential enzyme for the replication of HIV and has no closely related identified cellular homolog, it is regarded as one of the most important targets for the antiviral chemotherapy against HIV infections [2]. The nucleoside derivatives 3'-azido-3'-deoxythymidine (AZT) [3], 2',3'-dideoxyinosine (DDI) [4], 2',3'-dideoxycytidine (DDC) [5] and 2',3'-dideoxy-3'-deoxythymidine (d4T) [6], potent RT inhibitors of HIV, have been proven to improve the clinical and immunological status of patients with AIDS and AIDS-related complex. However, they also induce bone marrow suppression, peripheral neuropathy, pancreatitis, and other side effects [2]. Furthermore, prolonged treatment of these drugs often leads to the emergence of drug-resistant virus strains [2]. It seems, therefore, still imperative to find novel chemotherapeutic agents which are more potent and selective in their anti-HIV-1 activity, preferably, through a different mechanism of action.

Since the discovery of the acyclic 6-substituted uridine derivative 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-

thymine (HEPT, **1a**) as a novel lead for specific anti-HIV-1 agents [7], a number of HEPT analogs have been synthesized to increase its potency. Several of these compounds such as 6-[(3,5-dimethylphenyl)thio]-1-(ethoxymethyl)-5-ethyluracil **1b**, 1-(benzyloxymethyl)-6-[(3,5-dimethylphenyl)thio]-5-ethyluracil **1c**, and 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442, **1d**) inhibit HIV-1 replication in the nanomolar concentration range [8-10]. From synthetic studies of HEPT analogs, it has been found that the presence of the 2'-oxygen atom in the acyclic chain is not essential for anti-HIV-1 activity [8]. Recently, Goudgaon and Schinazi prepared a series of 6-phenylselenenyl analogs of HEPT and found that 1-[(2-hydroxyethoxy)methyl]-6-(phenylselenenyl)thymine **1e** was more active than HEPT against HIV-1 in primary human lymphocytes [11].

On the basis of these findings, we synthesized 1,5-dialkyl-6-(phenylselenenyl)uracils and -2-thiouracils

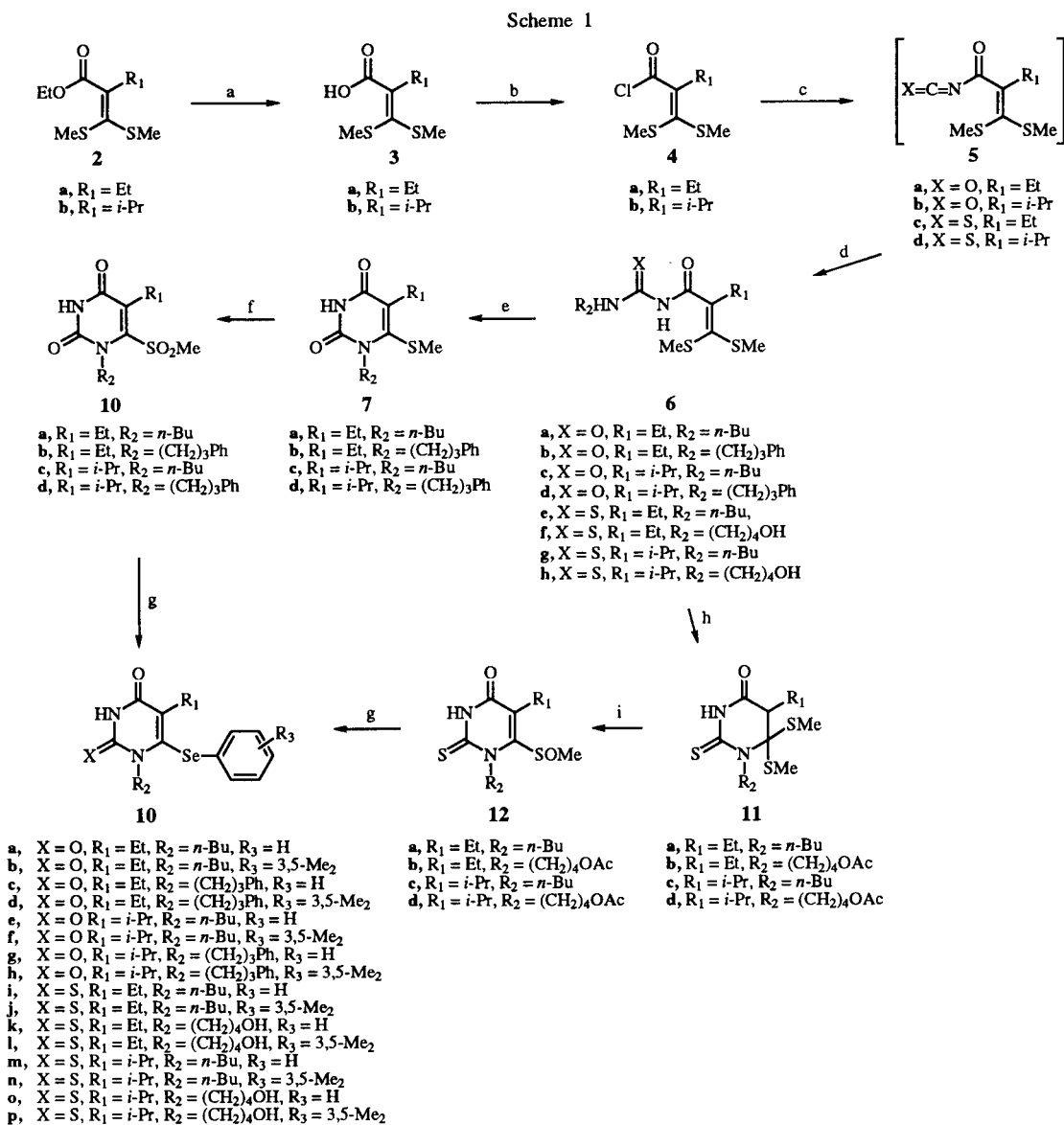


- a**, R₁ = Me, R₂ = CH₂OH, X = S, Y = H
b, R₁ = Et, R₂ = Me, X = S, Y = 3,5-Me₂
c, R₁ = Et, R₂ = Ph, X = S, Y = 3,5-Me₂
d, R₁ = *i*-Pr, R₂ = Me, X = CH₂, Y = H
e, R₁ = Me, R₂ = CH₂OH, X = Se, Y = H

which have been modified at the 3- and 5-positions of the C-6 phenylselenenyl ring with two methyl groups and evaluated their anti-HIV-1 activity.

The lithium diisopropylamide lithiation approach is highly efficient for the synthesis of various C-6-modified HEPT and HEPT-S analogs [7-9, 11,12]. This approach was, however, found not to be applicable to the synthesis of 6-substituted 1-alkyluracil derivatives, presumably due to the lack of an oxygen atom at the N-1 alkyl group which stabilizes the C-6 lithiated species [13]. Thus, 1-alkyl

analogs of HEPT were synthesized from HEPT analogs in a quite inefficient way which involves acid cleavage of the acyclic chain at the N-1 position followed by alkylation with an appropriate alkyl halide [8]. We have recently reported a general and convenient approach to the synthesis of 6-substituted 1,5-dialkyluracils and -2-thiouracils from readily accessible ethyl 2-alkyl-3,3-di(methylthio)acrylates, which could overcome the limitation of lithium diisopropylamide lithiation method [14]. Employing this approach, we synthesized 1,5-dialkyl-6-(arylselenenyl)uracils **10a-h** and

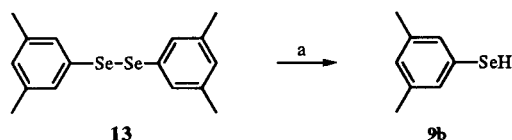


[a] 2*N* KOH (2 equivalents for **2a** or 4 equivalents for **2b**), EtOH, reflux, 3 hours (for **2a**) or 72 hours (for **2b**); [b] (COCl)₂ (1.2 equivalents), DMF (cat), benzene, rt, 3 hours, N₂ atmosphere; [c] AgOCN (1.05 equivalents) (for **5a-b**) or NH₄SCN (1.05 equivalents) (for **5c-d**), benzene, reflux, 0.5 hour, N₂ atmosphere; [d] R₂NH₂ (1.1 equivalents), benzene, -78° to rt over 1 hour (for **6a-d**) or -20° to rt over 1 hour (for **6e-h**); [e] methanesulfonic acid (0.2 equivalent), AcOH, 80°, 1 hour; [f] 3-chloroperoxybenzoic acid (5 equivalents), benzene, reflux, 16 hours; [g] benzeneselenol or (3,5-dimethylphenyl)selenol (1.1 equivalents), NaOH, EtOH, rt, 2 hours, N₂ atmosphere; [h] methanesulfonic acid (1.0 equivalent), AcOH, rt, 1.5 hours; [i] NaIO₄ (6.0 equivalents), H₂O, MeOH, reflux, 1.5 hours.

-2-thiouracils **10i-p** from ethyl 2-alkyl-3,3-di(methylthio)acrylates **2a-b** [15,16] as shown in Scheme 1.

Hydrolysis of esters **2a-b** with 2*N* ethanolic potassium hydroxide solution and subsequent reaction of the corresponding carboxylic acids **3a-b** with oxalyl chloride in benzene in the presence of a catalytic amount of *N,N*-dimethylformamide afforded 2-alkyl-3,3-(dimethylthio)acryloyl chlorides **4a-b** in two-step yields of 75-78%. Treatment of **4a-b** with either silver cyanate or ammonium thiocyanate in benzene followed by reaction of the resulting isocyanates **5a-b** or isothiocyanates **5c-d** with an appropriate amine gave *N*-alkyl-*N'*-[3,3-di(methylthio)-2-alkylacryloyl]ureas **6a-d** or -thioureas **6e-h** in good yields (77-91%). Cyclization of **6a-d** was accomplished in acetic acid containing a catalytic amount of methanesulfonic acid at 80° to give 1,5-dialkyl-6-(methylthio)uracils **7a-d** in 84-96% yields. Oxidation of **7a-d** with 3-chloroperoxybenzoic acid in refluxing benzene resulted in 88-98% yields of 1,5-dialkyl-6-(methylsulfonyl)uracils **8a-d**. Reaction of **8a-d** with either benzeneselenol (**9a**) or (3,5-dimethylphenyl)selenol (**9b**) in ethanolic sodium hydroxide solution afforded 1,5-dialkyl-6-(arylselenenyl)uracils **10a-h** in excellent yields (>94%). The required **9b** was prepared by reduction of bis(3,5-dimethylphenyl) diselenide (**13**) with zinc powder in a mixture of 6*N* hydrochloric acid and diethyl ether in 87% yield (Scheme 2).

Scheme 2



[a] Zn powder, 6*N* HCl, Et₂O, reflux, 1 hour, N₂ atmosphere.

In contrast to the acryloyl ureas, the acryloyl thioureas **6e-h** were cyclized in acetic acid containing 1 equivalent of methanesulfonic acid at room temperature to give 1,5-dialkyl-5,6-dihydro-6,6-di(methylthio)-2-thiouracils **11a-d** in good to excellent yields (88-99%). Treatment of **11a-d** with aqueous sodium periodate solution in methanol at reflux temperature produced 1,5-dialkyl-6-(methylsulfinyl)-2-thiouracils **12a-d** in fair yields (57-73%), which were reacted with either **9a** or **9b** in ethanolic sodium hydroxide solution to afford 1,5-dialkyl-6-(arylselenenyl)-2-thiouracils **10i-p** in fair to good yields (60-88%).

The anti-HIV-1 (HTLV-III_B) activity and cytotoxicity of the compounds **10a-p** were tested as previously described [17,18], and the results are summarized in Table 1 along with those of MKC-442, AZT, and DDC. All the uracil derivatives **10a-h** inhibited HIV-1 replication in MT-4 cells in the nanomolar concentration range. A considerable increase in anti-HIV-1 activity was accomplished by introducing two methyl substituents at the *meta* position of the

Table 1
Inhibition of HIV-1 Replication in MT-4 Cells by
1,5-Dialkyl-6-(arylselenenyl)uracils and -2-thiouracils [a]

Compound	EC ₅₀ [b] (μM)	CC ₅₀ [c] (μM)	SI [d]
10a	0.04	27.3	683
10b	0.003	27.9	9300
10c	0.003	26.1	8700
10d	0.008	27.7	3463
10e	0.002	27.1	13550
10f	0.002	28.2	14100
10g	0.008	28.0	3500
10h	0.0006	26.9	44833
10i	> 200	19.2	< 1
10j	> 200	25.8	< 1
10k	> 200	20.3	< 1
10l	> 200	35.2	< 1
10m	> 200	24.2	< 1
10n	> 200	22.9	< 1
10o	> 200	23.5	< 1
10p	> 200	24.3	< 1
MKC-442	0.006	31.6	5267
AZT	0.0046	18.7	4065
DDC	0.60	17.6	29

[a] The antiviral activity and cytotoxicity of the compound were tested by the National Institute of Health (Seoul, Korea). All data are the mean value of at least two independent experiments in duplicate. [b] Effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1. [c] Cytotoxic concentration of compound required to reduce the viability of mock-infected MT-4 cells by 50%. [d] Selective index: ratio of CC₅₀/EC₅₀.

6-phenylselenenyl ring without increasing the cytotoxicity of the compounds for some uracil derivatives as previously observed [12]. Thus, the 6-[(3,5-dimethylphenyl)selenenyl] derivatives **10b** and **10h** were 13.3-fold more potent than the corresponding 6-(phenylselenenyl) derivatives **10a** and **10g**, respectively. Among these, compound **10h** was the most inhibitory to HIV-1 replication with an EC₅₀ value of 0.0006 μM with a selective index of 44833, which is 10- and 7.7-fold more potent than MKC-442 and AZT, respectively. The previous studies of the structure-activity relationships of HEPT analogs indicated that replacement of the 2-oxo function with a thione function potentiated their anti-HIV-1 activity [8,19]. Surprisingly, the 2-thiouracil derivatives **10i-p**, however, did not show any anti-HIV-1 activity at concentrations up to 200 μM.

EXPERIMENTAL

Melting points were determined on either an Electrothermal F500MA digital or a Mettler FP62 melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. The ¹H nmr and ¹³C nmr spectra were run in deuteriochloroform on a Varian Unity 300 spectrometer. The chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane for ¹H nmr, and deuteriochloroform served as the internal standard at δ 77.0 for ¹³C nmr. The electron

impact mass spectra were obtained on a VG Quattro mass spectrometer. The tlc analysis was performed on Merck silica gel 60F-254 glass plates. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

General Procedure for the Preparation of 2-Alkyl-3,3-di(methylthio)acrylic Acids **3a-b**.

A mixture of ethyl 2-alkyl-3,3-di(methylthio)acrylate **2a-b** (300 mmoles) and 2*N* potassium hydroxide (300 ml for **2a** or 600 ml for **2b**) in ethanol (300 ml for **2a** or 1200 ml for **2b**) was heated under reflux for 3 hours (for **2a**) or 72 hours (for **2b**). The reaction mixture was concentrated to remove ethanol and poured into water (300 ml). The aqueous phase was washed with diethyl ether (2 x 200 ml), acidified with concentrated hydrochloric acid to pH 3, and extracted with diethyl ether (3 x 200 ml). The combined ethereal solution was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was crystallized from a suitable solvent to give **3a-b** as white crystals.

3,3-Di(methylthio)-2-ethylacrylic Acid (**3a**).

This compound was synthesized from **2a** in 86% yield, mp 69.8-70.5° (hexane); ir (potassium bromide): 1690 (CO) cm⁻¹; ¹H nmr: δ 1.10 (t, J = 7.5 Hz, 3H, CH₂CH₃), 2.37 (s, 6H, 2SCH₃), 2.69 (q, J = 7.5 Hz, 2H, CH₂CH₃), 11.48 (br s, 1H, COOH); ¹³C nmr: δ 13.3, 17.2, 18.2, 26.8, 138.9, 143.5, 172.8; ms: m/z 192 (M⁺).

Anal. Calcd. for C₇H₁₂O₂S₂: C, 43.72; H, 6.29. Found: C, 43.65; H, 6.35.

3,3-Di(methylthio)-2-isopropylacrylic Acid (**3b**).

This compound was synthesized from **2b** in 82% yield, mp 82.3-84.3° (hexane); ir (potassium bromide): 1690 (CO) cm⁻¹; ¹H nmr: δ 1.15 (d, J = 6.9 Hz, 6H, 2CH₃), 2.29 (s, 3H, SCH₃), 2.34 (s, 3H, SCH₃), 3.34 (septet, J = 6.9 Hz, 1H, CH); ¹³C nmr: δ 16.2, 17.8, 20.9, 31.9, 133.9, 146.9, 173.4; ms: m/z 206 (M⁺).

Anal. Calcd. for C₈H₁₄O₂S₂: C, 46.57; H, 6.84. Found: C, 46.48; H, 6.92.

General Procedure for the Preparation of 2-Alkyl-3,3-di(methylthio)acryloyl Chlorides **4a-b**.

To a stirred solution of 2-alkyl-3,3-di(methylthio)acrylic acid **3a-b** (100 mmoles) in anhydrous benzene (100 ml) were added oxalyl chloride (10.5 ml, 120 mmoles) dropwise and 3 drops of *N,N*-dimethylformamide at 0° under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 hours and evaporated to dryness. The residue was distilled *in vacuo* to give **4a-b** as a brick red oil.

3,3-Di(methylthio)-2-ethylacryloyl Chloride (**4a**).

This compound was synthesized from **3a** in 91% yield, bp 102-107° (2.5 mm Hg); ir (potassium bromide): 1786 (CO) cm⁻¹; ¹H nmr: δ 1.14 (t, J = 7.5 Hz, 3H, CH₂CH₃), 2.37 (s, 3H, SCH₃), 2.40 (s, 3H, SCH₃), 2.72 (q, J = 7.5 Hz, 2H, CH₂CH₃); ¹³C nmr: δ 12.9, 17.0, 18.0, 26.8, 143.1, 143.5, 166.5.

3,3-Di(methylthio)-2-isopropylacryloyl Chloride (**4b**).

This compound was synthesized from **3b** in 91% yield, bp 102-114° (1 mm Hg); ir (potassium bromide): 1786 (CO) cm⁻¹; ¹H nmr: δ 1.18 (d, J = 6.9 Hz, 6H, 2CH₃), 2.32 (s, 3H, SCH₃), 2.36 (s, 3H, SCH₃), 3.32 (septet, J = 6.9 Hz, 1H, CH); ¹³C nmr: δ 16.1, 17.6, 20.8, 32.4, 134.8, 151.2, 166.7.

General Procedure for the Preparation of *N*-Alkyl-*N'*-[3,3-di(methylthio)-2-alkylacryloyl]ureas **6a-d**.

A mixture of 2-alkyl-3,3-di(methylthio)acryloyl chloride **4a-b** (16.6 mmoles) and silver cyanate (2.61 g, 17.4 mmoles) in anhydrous benzene (30 ml) was heated under reflux for 30 minutes under a nitrogen atmosphere in the dark to generate isocyanate **5a-b in situ** and cooled to -78°. To this mixture was added alkylamine (18.3 mmoles) in anhydrous benzene (10 ml) in a dropwise manner. The mixture was allowed to warm to room temperature over 30 minutes and filtered through a pad of Celite, and the filtrate was again filtered using a millipore filter (0.22 μm). The filtrate was evaporated to dryness, and the residue was purified by flash column chromatography on silica gel with ethyl acetate-hexane as eluent and then crystallized from a suitable solvent.

N-Butyl-*N'*-[3,3-di(methylthio)-2-ethylacryloyl]urea (**6a**).

This compound was synthesized from **4a** with butylamine in 87% yield, mp 133.2-134.5° (ethyl acetate-hexane); ir (potassium bromide): 1665, 1690 (CO) cm⁻¹; ¹H nmr: δ 0.94 (t, J = 7.2 Hz, 3H, NCH₂CH₂CH₂CH₃), 1.07 (t, J = 7.5 Hz, 3H, CH₂CH₃), 1.39 (m, 2H, NCH₂CH₂CH₂), 1.58 (m, 2H, NCH₂CH₂), 2.31 (s, 3H, SCH₃), 2.34 (s, 3H, SCH₃), 2.62 (q, J = 7.5 Hz, 2H, CH₂CH₃), 3.31 (m, 2H, NCH₂), 8.27 (br s, 2H, 2NH); ¹³C nmr: δ 12.9, 13.7, 16.4, 17.7, 20.1, 27.2, 30.2, 45.5, 139.0, 142.3, 168.9, 179.5; ms: m/z 291 (M⁺ + H).

Anal. Calcd. for C₁₂H₂₂N₂O₂S₂: C, 49.63; H, 7.63; N, 9.65. Found: C, 49.42; H, 7.68; N, 9.53.

N-[3,3-Di(methylthio)-2-ethylacryloyl]-*N'*-(3-phenylpropyl)urea (**6b**).

This compound was synthesized from **4a** with 3-phenyl-1-propylamine in 91% yield, mp 117.2-117.5° (ethyl acetate-hexane); ir (potassium bromide): 1662, 1698 (CO) cm⁻¹; ¹H nmr: δ 1.06 (t, J = 7.5 Hz, 3H, CH₂CH₃), 1.92 (quintet, J = 7.5 Hz, 2H, NCH₂CH₂), 2.30 (s, 3H, SCH₃), 2.32 (s, 3H, SCH₃), 2.57-2.73 (m, 4H, CH₂Ph and CH₂CH₃), 3.33 (dd, J = 12.9 Hz, J = 6.9 Hz, 2H, NCH₂), 7.12-7.33 (m, 5H, Ar H), 8.37 (br s, 1H, NH), 8.49 (br s, 1H, NH); ¹³C nmr: δ 12.8, 16.3, 17.5, 27.1, 31.1, 33.1, 39.4, 125.9, 128.3, 128.4, 136.5, 141.3, 143.9, 153.9, 170.5; ms: m/z 353 (M⁺).

Anal. Calcd. for C₁₇H₂₄N₂O₂S₂: C, 57.92; H, 6.86; N, 7.95. Found: C, 57.81; H, 6.95; N, 7.72.

N-Butyl-*N'*-[3,3-di(methylthio)-2-isopropylacryloyl]urea (**6c**).

This compound was synthesized from **4b** with butylamine in 84% yield, mp 113.6-114.2° (ethyl acetate-hexane); ir (potassium bromide): 1674, 1696 (CO) cm⁻¹; ¹H nmr: δ 0.94 (t, J = 7.2 Hz, 3H, NCH₂CH₂CH₂CH₃), 1.11 (d, J = 6.9 Hz, 6H, CH(CH₃)₂), 1.38 (m, 2H, NCH₂CH₂CH₂), 1.57 (m, 2H, NCH₂CH₂), 2.26 (s, 3H, SCH₃), 2.32 (s, 3H, SCH₃), 3.23-3.40 (m, 3H, NCH₂ and CH(CH₃)₂), 8.32 (br s, 1H, NH), 8.83 (br s, 1H, NH); ¹³C nmr: δ 13.8, 16.3, 17.3, 20.1, 21.1, 31.6, 32.3, 39.6, 133.8, 149.1, 153.8, 169.6; ms: m/z 305 (M⁺ + H).

Anal. Calcd. for C₁₃H₂₄N₂O₂S₂: C, 51.28; H, 7.94; N, 9.20. Found: C, 51.32; H, 7.99; N, 9.02.

N-[3,3-Di(methylthio)-2-isopropylacryloyl]-*N'*-(3-phenylpropyl)urea (**6d**).

This compound was synthesized from **4b** with 3-phenyl-1-propylamine in 88% yield, mp 102.9-104.0° (ethyl acetate-hexane); ir (potassium bromide): 1675, 1695 (CO) cm⁻¹; ¹H nmr:

δ 1.11 (d, $J = 6.9$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.92 (quintet, $J = 7.5$ Hz, 2H, NCH_2CH_2), 2.26 (s, 3H, SCH_3), 2.31 (s, 3H, SCH_3), 2.69 (t, $J = 7.8$ Hz, 2H, CH_2Ph), 3.25-3.40 (m, 3H, NCH_2 and $\text{CH}(\text{CH}_3)_2$), 7.15-7.33 (m, 5H, Ar H), 8.38 (br s, 1H, NH), 8.58 (br s, 1H, NH); ^{13}C nmr: δ 16.2, 17.4, 21.1, 31.1, 32.3, 33.1, 39.4, 125.9, 128.3, 128.4, 134.0, 141.3, 149.0, 153.7, 169.6; ms: m/z 366 (M^+ - H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2\text{S}_2$: C, 58.98; H, 7.15; N, 7.64. Found: C, 59.16; H, 7.31; N, 7.48.

General Procedure for the Preparation of *N*-Alkyl-*N'*-[3,3-di(methylthio)-2-alkylacryloyl]thioureas **6e-h**.

A mixture of 2-alkyl-3,3-di(methylthio)acryloyl chloride **4a-b** (24.7 mmoles) and ammonium thiocyanate (1.97 g, 25.9 mmoles) in anhydrous benzene (30 ml) was heated under reflux for 30 minutes under a nitrogen atmosphere in the dark to generate thioisocyanate **5c-d** *in situ* and cooled to -20° . To this mixture was added alkylamine (27.2 mmoles) in anhydrous benzene (10 ml) in a dropwise manner. After stirring at room temperature for 1 hour, the mixture was poured into water (40 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic phase was washed with brine (50 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with ethyl acetate-hexane as eluent and then crystallized from a suitable solvent.

N-Butyl-*N'*-[3,3-di(methylthio)-2-ethylacryloyl]thiourea (**6e**).

This compound was synthesized from **4a** with butylamine in 85% yield, mp $98.2-99.8^\circ$ (ethanol); ir (potassium bromide): 1671 (CO) cm^{-1} ; ^1H nmr: δ 0.97 (t, $J = 7.2$ Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.07 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 1.43 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.68 (m, 2H, NCH_2CH_2), 2.35 (s, 3H, SCH_3), 2.36 (s, 3H, SCH_3), 2.63 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 3.66 (m, 2H, NCH_2), 9.15 (br s, 1H, NH), 10.43 (br s, 1H, NH); ^{13}C nmr: δ 12.9, 13.7, 16.4, 17.7, 20.1, 27.2, 30.2, 45.5, 139.0, 142.4, 169.0, 179.5; ms: m/z 307 (M^+ + H).

Anal. Calcd. for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{OS}_3$: C, 47.03; H, 7.23; N, 9.14. Found: C, 47.12; H, 7.28; N, 9.02.

N-[3,3-Di(methylthio)-2-ethylacryloyl]-*N'*-(4-hydroxybutyl)thiourea (**6f**).

This compound was synthesized from **4a** with 4-amino-1-butanol in 80% yield, mp $68.1-70.6^\circ$ (ethyl acetate-hexane); ir (potassium bromide): 1663 (CO), 3385 (OH) cm^{-1} ; ^1H nmr: δ 1.07 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 1.55 (br s, 1H, OH), 1.67 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.82 (m, 2H, NCH_2CH_2), 2.36 (s, 6H, 2SCH_3), 2.63 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 3.62-3.80 (m, 4H, NCH_2 and CH_2OH), 8.96 (br s, 1H, NH), 10.47 (br s, 1H, NH); ^{13}C nmr: δ 12.9, 16.3, 17.7, 24.7, 27.2, 29.8, 45.3, 62.1, 138.9, 142.3, 169.0, 179.7; ms: m/z 323 (M^+).

Anal. Calcd. for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}_2\text{S}_3$: C, 44.69; H, 6.88; N, 8.69. Found: C, 44.35; H, 6.99; N, 8.63.

N-Butyl-*N'*-[3,3-di(methylthio)-2-isopropylacryloyl]thiourea (**6g**).

This compound was synthesized from **4b** with butylamine in 81% yield, mp $85.9-86.4^\circ$ (ethanol); ir (potassium bromide): 1670 (CO) cm^{-1} ; ^1H nmr: δ 0.97 (t, $J = 7.4$ Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.13 (d, $J = 6.9$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.43 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.69 (m, 2H, NCH_2CH_2), 2.31 (s, 3H, SCH_3), 2.35 (s, 3H, SCH_3), 3.33 (septet, $J = 6.9$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 3.66 (m, 2H, NCH_2), 8.80 (br s, 1H, NH), 10.40 (br s, 1H, NH); ^{13}C nmr: δ 13.7, 16.2, 17.4, 20.1, 21.1, 30.2, 32.5, 45.5, 135.7, 147.9, 168.6, 179.4; ms: m/z 321 (M^+ - H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{24}\text{N}_2\text{OS}_3$: C, 48.71; H, 7.55; N, 8.74. Found: C, 48.82; H, 7.71; N, 8.58.

N-[3,3-Di(methylthio)-2-isopropylacryloyl]-*N'*-(4-hydroxybutyl)thiourea (**6h**).

This compound was synthesized from **4b** with 4-amino-1-butanol in 77% yield, mp $93.7-94.0^\circ$ (ethyl acetate-hexane); ir (potassium bromide): 1666 (CO), 3253 (OH) cm^{-1} ; ^1H nmr: δ 1.13 (d, $J = 6.9$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.60-1.73 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.82 (m, 2H, NCH_2CH_2), 2.31 (s, 3H, SCH_3), 2.35 (s, 3H, SCH_3), 3.33 (septet, $J = 6.9$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 3.64-3.76 (m, 4H, NCH_2 and CH_2OH), 8.84 (br s, 1H, NH), 10.46 (br s, 1H, NH); ^{13}C nmr: δ 16.2, 17.4, 21.1, 24.7, 29.8, 32.5, 45.3, 62.2, 135.7, 147.8, 168.6, 179.6; ms: m/z 337 (M^+).

Anal. Calcd. for $\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_2\text{S}_3$: C, 46.40; H, 7.19; N, 8.32. Found: C, 46.52; H, 7.31; N, 8.15.

General Procedure for the Preparation of 1,5-Dialkyl-6-(methylthio)uracils **7a-d**.

A stirred suspension of *N*-alkyl-*N'*-[3,3-di(methylthio)-2-alkylacryloyl]urea **6a-d** (1.72 mmole) and methanesulfonic acid (25.0 mg, 0.26 mmole) in acetic acid (10 ml) was heated at 80° for 1 hour. The reaction mixture was evaporated to dryness, and the residue was dissolved in dichloromethane (50 ml). The dichloromethane solution was washed with saturated sodium bicarbonate solution (25 ml) and brine (25 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with ethyl acetate-hexane as eluent and then crystallized from a suitable solvent.

1-Butyl-5-ethyl-6-(methylthio)uracil (**7a**).

This compound was synthesized from **6a** in 96% yield, mp $133.2-134.5^\circ$ (ethyl acetate); ir (potassium bromide): 1663, 1682 (CO) cm^{-1} ; ^1H nmr: δ 0.96 (t, $J = 7.4$ Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.13 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 1.38 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.65 (m, 2H, NCH_2CH_2), 2.41 (s, 3H, SCH_3), 2.71 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 4.13 (t, $J = 7.8$ Hz, 2H, NCH_2), 8.66 (br s, 1H, NH); ^{13}C nmr: δ 13.7, 14.1, 19.9, 20.1, 22.2, 31.5, 46.5, 124.0, 149.2, 150.7, 162.1; ms: m/z 242 (M^+).

Anal. Calcd. for $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: C, 54.52; H, 7.49; N, 11.56. Found: C, 54.27; H, 7.61; N, 11.48.

5-Ethyl-6-(methylthio)-1-(3-phenylpropyl)uracil (**7b**).

This compound was synthesized from **6b** in 93% yield, mp $119.4-120.2^\circ$ (ethyl acetate); ir (potassium bromide): 1667 (CO) cm^{-1} ; ^1H nmr: δ 1.11 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 2.03 (tt, $J = 7.8$ Hz, $J = 7.5$ Hz, 2H, NCH_2CH_2), 2.32 (s, 3H, SCH_3), 2.67 (t, $J = 7.5$ Hz, 2H, CH_2Ph), 2.70 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 4.16 (t, $J = 7.8$ Hz, 2H, NCH_2), 7.19-7.31 (m, 5H, Ar H), 8.90 (br s, 1H, NH); ^{13}C nmr: δ 14.0, 20.0, 22.2, 30.5, 32.9, 46.4, 124.1, 126.1, 128.3, 128.4, 140.8, 149.0, 150.6, 161.9; ms: m/z 304 (M^+).

Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$: C, 63.13; H, 6.62; N, 9.20. Found: C, 63.20; H, 6.51; N, 9.04.

1-Butyl-5-isopropyl-6-(methylthio)uracil (**7c**).

This compound was synthesized from **6c** in 84% yield, mp $118.6-119.5^\circ$ (ethyl acetate-hexane); ir (potassium bromide): 1646, 1699 (CO) cm^{-1} ; ^1H nmr: δ 0.96 (t, $J = 7.4$ Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.33 (d, $J = 6.9$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.39 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.64 (m, 2H, NCH_2CH_2), 2.40 (s, 3H,

SCH₃), 3.54 (septet, *J* = 6.9 Hz, 1H, CH(CH₃)₂), 4.15 (t, *J* = 7.8 Hz, 2H, NCH₂), 8.77 (br s, 1H, NH); ¹³C nmr: δ 13.8, 19.9, 20.3, 20.6, 31.6, 31.7, 46.7, 126.4, 149.1, 150.6, 161.2; ms: *m/z* 257 (M⁺ + H).

Anal. Calcd. for C₁₂H₂₀N₂O₂S: C, 56.22; H, 7.86; N, 10.93. Found: C, 56.03; H, 7.93; N, 10.88.

5-Isopropyl-6-(methylthio)-1-(3-phenylpropyl)uracil (7d).

This compound was synthesized from **6d** in 86% yield, mp 93.4-94.4° (ethyl acetate-hexane); ir (potassium bromide): 1682, 1694 (CO) cm⁻¹; ¹H nmr: δ 1.31 (d, *J* = 6.9 Hz, 6H, CH(CH₃)₂), 2.01 (tt, *J* = 7.8 Hz, *J* = 7.7 Hz, 2H, NCH₂CH₂), 2.32 (s, 3H, SCH₃), 2.70 (t, *J* = 7.7 Hz, 2H, CH₂Ph), 3.51 (septet, *J* = 6.9 Hz, 1H, CH(CH₃)₂), 4.18 (t, *J* = 7.8 Hz, 2H, NCH₂), 7.16-7.31 (m, 5H, Ar H), 8.55 (br s, 1H, NH); ¹³C nmr: δ 20.2, 20.5, 30.7, 31.7, 32.9, 46.5, 126.1, 126.5, 128.3, 128.4, 140.8, 148.9, 150.5, 161.0; ms: *m/z* 318 (M⁺).

Anal. Calcd. for C₁₇H₂₂N₂O₂S: C, 64.12; H, 6.96; N, 8.80. Found: C, 64.25; H, 7.00; N, 8.58.

General Procedure for the Preparation of 1,5-Dialkyl-6-(methylsulfonyl)uracils **8a-d**.

A mixture of 1,5-dialkyl-6-(methylthio)uracil **7a-d** (6.2 mmoles) and 3-chloroperoxybenzoic acid (85%, 6.29 g, 31.0 mmoles) in benzene (50 ml) was heated under reflux for 16 hours. The reaction mixture was evaporated to dryness, and the residue was dissolved in water (50 ml). The aqueous phase was extracted with ethyl acetate (3 x 50 ml). The combined ethyl acetate solution was washed with saturated sodium bicarbonate solution (50 ml) and brine (50 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with ethyl acetate-hexane (1:2) as eluent and then crystallized from a suitable solvent.

1-Butyl-5-ethyl-6-(methylsulfonyl)uracil (8a).

This compound was synthesized from **7a** in 98% yield, mp 167.7° dec (ethyl acetate); ir (potassium bromide): 1149 (SO₂), 1688 (CO) cm⁻¹; ¹H nmr: δ 0.95 (t, *J* = 7.4 Hz, 3H, NCH₂CH₂CH₂CH₃), 1.19 (t, *J* = 7.2 Hz, 3H, CH₂CH₃), 1.36 (m, 2H, NCH₂CH₂CH₂), 1.72 (m, 2H, NCH₂CH₂), 2.90 (q, *J* = 7.2 Hz, 2H, CH₂CH₃), 3.23 (s, 3H, SO₂CH₃), 4.21 (t, *J* = 7.8 Hz, 2H, NCH₂), 9.17 (br s, 1H, NH); ¹³C nmr: δ 13.6, 14.3, 19.9, 20.4, 31.5, 45.3, 47.6, 124.5, 147.9, 150.1, 162.1; ms: *m/z* 274 (M⁺).

Anal. Calcd. for C₁₁H₁₈N₂O₄S: C, 48.16; H, 6.61; N, 10.21. Found: C, 47.92; H, 6.68; N, 10.15.

5-Ethyl-6-(methylsulfonyl)-1-(3-phenylpropyl)uracil (8b).

This compound was synthesized from **7b** in 93% yield, mp 143.3-145.3° (ethyl acetate-hexane); ir (potassium bromide): 1150 (SO₂), 1690 (CO) cm⁻¹; ¹H nmr: δ 1.17 (t, *J* = 7.4 Hz, 3H, CH₂CH₃), 2.10 (tt, *J* = 7.8 Hz, *J* = 7.7 Hz, 2H, NCH₂CH₂), 2.69 (t, *J* = 7.7 Hz, 2H, CH₂Ph), 2.86 (q, *J* = 7.4 Hz, 2H, CH₂CH₃), 3.10 (s, 3H, SO₂CH₃), 4.23 (t, *J* = 7.8 Hz, 2H, NCH₂), 7.18-7.33 (m, 5H, Ar H), 9.01 (br s, 1H, NH); ¹³C nmr: δ 14.3, 20.4, 30.7, 32.8, 45.1, 47.5, 124.7, 126.1, 128.3, 128.4, 140.6, 147.8, 150.2, 162.1; ms: *m/z* 337 (M⁺ + H).

Anal. Calcd. for C₁₆H₂₀N₂O₄S: C, 57.13; H, 5.99; N, 8.33. Found: C, 57.02; H, 6.05; N, 8.21.

1-Butyl-5-isopropyl-6-(methylsulfonyl)uracil (8c).

This compound was synthesized from **7c** in 88% yield, mp 183.7-184.0° (ethyl acetate-hexane); ir (potassium bromide): 1154 (SO₂), 1676, 1696 (CO) cm⁻¹; ¹H nmr: δ 0.95 (t, *J* = 7.4 Hz, 3H, NCH₂CH₂CH₂CH₃), 1.34 (m, 2H, NCH₂CH₂CH₂), 1.38 (d, *J* = 6.9 Hz, 6H, CH(CH₃)₂), 1.73 (m, 2H, NCH₂CH₂), 3.26 (s, 3H, SO₂CH₃), 3.76 (septet, *J* = 6.9 Hz, 1H, CH(CH₃)₂), 4.21 (t, *J* = 7.8 Hz, 2H, NCH₂), 8.92 (br s, 1H, NH); ¹³C nmr: δ 13.6, 19.9, 20.0, 28.9, 31.7, 46.0, 48.1, 127.5, 149.2, 150.4, 160.9; ms: *m/z* 288 (M⁺).

Anal. Calcd. for C₁₂H₂₀N₂O₄S: C, 49.98; H, 6.99; N, 9.71. Found: C, 50.13; H, 7.08; N, 9.56.

5-Isopropyl-6-(methylsulfonyl)-1-(3-phenylpropyl)uracil (8d).

This compound was synthesized from **7d** in 95% yield, mp 155.7-156.7° (ethyl acetate-hexane); ir (potassium bromide): 1154 (SO₂), 1688 (CO) cm⁻¹; ¹H nmr: δ 1.37 (d, *J* = 6.9 Hz, 6H, CH(CH₃)₂), 2.11 (quintet, *J* = 7.7 Hz, 2H, NCH₂CH₂), 2.67 (t, *J* = 7.7 Hz, 2H, CH₂Ph), 3.13 (s, 3H, SO₂CH₃), 3.72 (septet, *J* = 6.9 Hz, 1H, CH(CH₃)₂), 4.22 (t, *J* = 7.7 Hz, 2H, NCH₂), 7.14-7.33 (m, 5H, Ar H), 8.85 (br s, 1H, NH); ¹³C nmr: δ 20.0, 29.0, 30.9, 32.9, 45.8, 48.0, 126.1, 127.8, 128.4, 128.5, 140.7, 149.1, 150.3, 160.8; ms: *m/z* 351 (M⁺ + H).

Anal. Calcd. for C₁₇H₂₂N₂O₄S: C, 58.27; H, 6.33; N, 7.99. Found: C, 58.16; H, 6.42; N, 7.92

(3,5-Dimethylphenyl)selenol (9b).

A mixture of bis(3,5-dimethylphenyl) diselenide **13** (3.68 g, 10 mmoles) in 6*N* hydrochloric acid (20 ml) and diethyl ether (20 ml) was heated at diethyl ether boiling point. To this mixture was added zinc powder (0.65 g) in portions under a nitrogen atmosphere, and then the mixture was heated under reflux for 1 hour to give a colorless mixture. After cooling to room temperature, the ethereal solution was separated and extracted with 2*N* sodium hydroxide solution (2 x 5 ml). The sodium hydroxide solution was washed with diethyl ether (10 ml), acidified with 4*N* hydrochloric acid, and extracted with diethyl ether (2 x 20 ml) quickly. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was distilled *in vacuo* to give 3.22 g (87%) of **9b** as a colorless liquid, bp 68° (1 mm Hg); ir (neat): 1599 cm⁻¹; ¹H nmr: δ 1.43 (s, 1H, SeH), 2.25 (s, 6H, 2CH₃), 6.82 (m, 1H, Ar H); 7.06 (m, 2H, Ar H); ¹³C nmr: δ 21.1, 123.9, 128.2, 130.3, 138.9; ms: *m/z* 185 (M⁺).

General Procedure for the Preparation of 1,5-Dialkyl-5,6-dihydro-6,6-di(methylthio)-2-thiouracils **11a-d**.

A suspension of *N*-Alkyl-*N'*-[3,3-di(methylthio)-2-alkylacryloyl]thiourea **6e-h** (14.0 mmoles) and methanesulfonic acid (1.35 g, 14.0 mmoles) in acetic acid (50 ml) was stirred at room temperature for 1.5 hour. The reaction mixture was evaporated to dryness, and the residue was dissolved in dichloromethane (150 ml). The dichloromethane solution was washed with saturated sodium bicarbonate solution (50 ml) and brine (50 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with ethyl acetate-hexane as eluent.

1-Butyl-5,6-dihydro-6,6-di(methylthio)-5-ethyl-2-thiouracil (11a).

This compound was synthesized from **6e** in 99% yield, mp 116.1-120.0° (ethyl acetate-hexane); ir (potassium bromide): 1652 (CO) cm⁻¹; ¹H nmr: δ 0.93 (t, *J* = 7.4 Hz, 3H,

$\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.04 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 1.37 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.60 (m, 2H, NCH_2CH_2), 1.74 (m, 1H, CH_2CH_3), 2.03 (m, 1H, CH_2CH_3), 2.16 (s, 3H, SCH_3), 2.25 (s, 3H, SCH_3), 2.77 (dd, $J = 10.8$ Hz, $J = 3.6$ Hz, 1H, H-5), 3.33 (m, 2H, NCH_2), 9.08 (br s, 1H, NH); ^{13}C nmr: δ 12.4, 12.6, 13.7, 14.0, 20.0, 21.1, 31.8, 44.2, 52.3, 69.7, 163.4, 175.7; ms: m/z 307 ($\text{M}^+ + \text{H}$).

Anal. Calcd. for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{OS}_3$: C, 47.03; H, 7.23; N, 9.14. Found: C, 47.19; H, 7.38; N, 8.95.

1-(4-Acetoxybutyl)-5,6-dihydro-6,6-di(methylthio)-5-ethyl-2-thiouracil (**11b**).

This compound was synthesized from **6f** in 88% yield; ir (neat): 1648 (CO), 1737 (CO_2) cm^{-1} ; ^1H nmr: δ 1.03 (t, $J = 7.4$ Hz, 3H, CH_2CH_3), 1.63-1.84 (m, 5H, $\text{NCH}_2\text{CH}_2\text{CH}_2$ and 1H of CH_2CH_3), 1.97-2.13 (m, 1H, CH_2CH_3), 2.04 (s, 3H, COCH_3), 2.16 (s, 3H, SCH_3), 2.25 (s, 3H, SCH_3), 2.75 (dd, $J = 10.8$ Hz, $J = 3.6$ Hz, 1H, H-5), 3.40 (br s, 2H, NCH_2), 4.08 (t, $J = 5.4$ Hz, 2H, CH_2OAc); ^{13}C nmr: δ 12.4, 12.6, 14.0, 20.9, 21.0, 25.9, 29.6, 44.0, 52.4, 63.9, 69.7, 163.2, 171.0, 175.5; ms: m/z 365 (M^+).

Anal. Calcd. for $\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}_3\text{S}_3$: C, 46.13; H, 6.64; N, 7.68. Found: C, 45.88; H, 6.85; N, 7.63.

1-Butyl-5,6-dihydro-6,6-di(methylthio)-5-isopropyl-2-thiouracil (**11c**).

This compound was synthesized from **6g** in 99% yield, mp 138.9-139.8° (ethyl acetate); ir (potassium bromide): 1633 (CO) cm^{-1} ; ^1H nmr: δ 0.92 (t, $J = 7.2$ Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.02 (d, $J = 6.6$ Hz, 3H, CHCH_3), 1.18 (d, $J = 6.6$ Hz, 3H, CHCH_3), 1.37 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.60 (m, 2H, NCH_2CH_2), 2.13 (s, 3H, SCH_3), 2.25 (s, 3H, SCH_3), 2.44 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.78 (d, $J = 3.3$ Hz, 1H, H-5), 3.36 (br s, 2H, NCH_2), 9.62 (br s, 1H, NH); ^{13}C nmr: δ 12.6, 13.8, 14.2, 20.1, 20.2, 25.0, 28.1, 32.0, 44.6, 56.2, 69.8, 162.1, 174.4; ms: m/z 321 (M^+).

Anal. Calcd. for $\text{C}_{13}\text{H}_{24}\text{N}_2\text{OS}_3$: C, 48.71; H, 7.55; N, 8.74. Found: C, 48.85; H, 7.62; N, 8.61.

1-(4-Acetoxybutyl)-5,6-dihydro-6,6-di(methylthio)-5-isopropyl-2-thiouracil (**11d**).

This compound was synthesized from **6h** in 94% yield, mp 84.3-85.0° (ethyl acetate); ir (potassium bromide): 1644 (CO), 1742 (CO_2) cm^{-1} ; ^1H nmr: δ 1.04 (d, $J = 6.6$ Hz, 3H, CHCH_3), 1.19 (d, $J = 6.6$ Hz, 3H, CHCH_3), 1.69 (m, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.05 (s, 3H, COCH_3), 2.13 (s, 3H, SCH_3), 2.25 (s, 3H, SCH_3), 2.46 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.82 (d, $J = 2.7$ Hz, 1H, H-5), 3.36 (br s, 2H, NCH_2), 4.08 (br s, 2H, CH_2OAc); ^{13}C nmr: δ 12.8, 14.3, 20.1, 21.0, 25.0, 26.1, 26.7, 28.3, 46.0, 56.9, 64.1, 69.4, 156.7, 171.1, 172.4; ms: m/z 379 (M^+).

Anal. Calcd. for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_3\text{S}_3$: C, 47.59; H, 6.92; N, 7.40. Found: C, 47.71; H, 6.99; N, 7.25.

General Procedure for the Preparation of 1,5-Dialkyl-6-(methylsulfinyl)-2-thiouracils **12a-d**.

To a stirred solution of 1,5-dialkyl-5,6-dihydro-6,6-di(methylthio)-2-thiouracil **11a-d** (4.0 mmoles) in methanol (50 ml) was added a solution of sodium periodate (5.14 g, 24.0 mmoles) in water (50 ml) at room temperature. The mixture was heated under reflux for 1.5 hour and filtered. The filtrate was concentrated to 50 ml in volume. The concentrate was extracted by using continuous extractor with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash

column chromatography on silica gel with methanol-chloroform as eluent and then crystallized from a suitable solvent.

1-Butyl-5-ethyl-6-(methylsulfinyl)-2-thiouracil (**12a**).

This compound was synthesized from **11a** in 73% yield, mp 138.6-140.6° (ethyl acetate); ir (potassium bromide): 1042 (SO), 1633 (CO) cm^{-1} ; ^1H nmr: δ 0.95 (t, $J = 7.4$ Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.15 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 1.42 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.65 (m, 2H, NCH_2CH_2), 2.65 (m, 2H, CH_2CH_3), 2.85 (s, 3H, SOCH_3), 3.52 (br s, 2H, NCH_2), 6.63 (br s, 1H, NH).

Anal. Calcd. for $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_2\text{S}_2$: C, 48.15; H, 6.61; N, 10.21. Found: C, 48.20; H, 6.76; N, 10.11.

1-(4-Acetoxybutyl)-5-ethyl-6-(methylsulfinyl)-2-thiouracil (**12b**).

This compound was synthesized from **11b** in 70% yield, mp 112.5-114.3° (ethyl acetate-hexane); ir (potassium bromide): 1054 (SO), 1630 (CO), 1734 (CO_2) cm^{-1} ; ^1H nmr: δ 1.15 (t, $J = 7.4$ Hz, 3H, CH_2CH_3), 1.73 (br s, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.06 (s, 3H, COCH_3), 2.64 (m, 2H, CH_2CH_3), 2.86 (s, 3H, SOCH_3), 3.58 (br s, 2H, NCH_2), 4.10 (t, $J = 5.7$ Hz, 2H, CH_2OAc), 6.94 (br s, 1H, NH).

Anal. Calcd. for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_4\text{S}_2$: C, 46.97; H, 6.06; N, 8.43. Found: C, 46.72; H, 6.02; N, 8.61.

1-Butyl-5-isopropyl-6-(methylsulfinyl)-2-thiouracil (**12c**).

This compound was synthesized from **11c** in 63% yield, mp 123.0-123.6° (ethyl acetate); ir (potassium bromide): 1052 (SO), 1643 (CO) cm^{-1} ; ^1H nmr: δ 0.94 (t, $J = 7.2$ Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.36 (d, $J = 7.8$ Hz, 3H, CHCH_3), 1.39 (d, $J = 7.2$ Hz, 3H, CHCH_3), 1.41 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.64 (m, 2H, NCH_2CH_2), 2.83 (s, 3H, SOCH_3), 2.90 (septet, $J = 6.9$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 3.50 (br s, 2H, NCH_2), 6.57 (br s, 1H, NH); ^{13}C nmr: δ 13.7, 19.9, 20.0, 20.7, 31.0, 32.9, 42.0, 42.7, 102.2, 136.1, 149.9, 152.4; ms: m/z 289 ($\text{M}^+ + \text{H}$).

Anal. Calcd. for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_2\text{S}_2$: C, 49.97; H, 6.99; N, 9.71. Found: C, 50.05; H, 7.03; N, 9.81.

1-(4-Acetoxybutyl)-5-isopropyl-6-(methylsulfinyl)-2-thiouracil (**12d**).

This compound was synthesized from **11d** in 57% yield, mp 124.7-125.2° (ethyl acetate-hexane); ir (potassium bromide): 1060 (SO), 1622 (CO), 1737 (CO_2) cm^{-1} ; ^1H nmr: δ 1.36 (d, $J = 7.5$ Hz, 3H, CHCH_3), 1.38 (d, $J = 7.2$ Hz, 3H, CHCH_3), 1.73 (br s, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.05 (s, 3H, COCH_3), 2.83 (s, 3H, SOCH_3), 2.90 (septet, $J = 6.6$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 3.56 (br s, 2H, NCH_2), 4.10 (t, $J = 5.9$ Hz, 2H, CH_2OAc), 6.81 (br s, 1H, NH); ^{13}C nmr: δ 19.9, 20.7, 21.0, 25.6, 26.0, 33.0, 42.0, 42.5, 63.8, 136.1, 150.0, 152.4, 171.1; ms: m/z 347 ($\text{M}^+ + \text{H}$).

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_4\text{S}_2$: C, 48.54; H, 6.40; N, 8.09. Found: C, 48.72; H, 6.32; N, 7.85.

General Procedure for the Preparation of 1,5-Dialkyl-6-(arylselenenyl)uracils **10a-h** and -2-thiouracils **10i-p**.

To a stirred suspension of 1,5-dialkyl-6-(methylsulfonyl)-uracil **8a-d** or 1,5-dialkyl-6-(methylsulfinyl)-2-thiouracil **12a-d** (1.00 mmole) and arylselenol (1.10 mmoles) in ethanol (5 ml) was added 1N ethanolic sodium hydroxide solution (3.00 ml) at room temperature under a nitrogen atmosphere. After the mixture was stirred for 2 hours, 3N hydrochloric acid in ethanol (1.00 ml) was added, and the reaction mixture was evaporated to

dryness. The residue was purified by flash column chromatography on silica gel with methanol-chloroform as eluent and then crystallized from a suitable solvent.

1-Butyl-5-ethyl-6-(phenylselenenyl)uracil (10a).

This compound was synthesized from **8a** with benzeneselenol in 95% yield, mp 102.3-103.3° (ethyl acetate); ir (potassium bromide): 1654, 1706 (CO) cm^{-1} ; ^1H nmr: δ 0.87 (t, J = 7.2 Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.03 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.26 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.51 (m, 2H, NCH_2CH_2), 2.75 (q, J = 7.4 Hz, 2H, CH_2CH_3), 4.03 (t, J = 8.0 Hz, 2H, NCH_2), 7.31 (m, 5H, Ar H), 8.74 (br s, 1H, NH); ms: m/z 352 (M^+ + H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2\text{Se}$: C, 54.70; H, 5.74; N, 7.97. Found: C, 54.85; H, 5.62; N, 7.85.

1-Butyl-6-[(3,5-dimethylphenyl)selenenyl]-5-ethyluracil (10b).

This compound was synthesized from **8a** with (3,5-dimethylphenyl)selenol in 94% yield, mp 122.9-123.8° (ethyl acetate); ir (potassium bromide): 1662, 1701 (CO) cm^{-1} ; ^1H nmr: δ 0.87 (t, J = 7.2 Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.04 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.26 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.49 (m, 2H, NCH_2CH_2), 2.28 (s, 6H, 2CH_3), 2.76 (q, J = 7.4 Hz, 2H, CH_2CH_3), 4.04 (t, J = 8.0 Hz, 2H, NCH_2), 6.92 (s, 3H, Ar H), 8.68 (br s, 1H, NH); ms: m/z 380 (M^+ + H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_2\text{Se}$: C, 56.99; H, 6.38; N, 7.38. Found: C, 56.82; H, 6.35; N, 7.26.

5-Ethyl-1-(3-phenylpropyl)-6-(phenylselenenyl)uracil (10c).

This compound was synthesized from **8b** with benzeneselenol in 96% yield, mp 141.7-142.9° (ethyl acetate); ir (potassium bromide): 1675, 1684 (CO) cm^{-1} ; ^1H nmr: δ 1.04 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.91 (tt, J = 7.8 Hz, J = 7.5 Hz, 2H, NCH_2CH_2), 2.60 (t, J = 7.5 Hz, 2H, CH_2Ph), 2.74 (q, J = 7.4 Hz, 2H, CH_2CH_3), 4.03 (t, J = 7.8 Hz, 2H, NCH_2), 7.07-7.32 (m, 10H, Ar H), 8.56 (br s, 1H, NH); ms: m/z 414 (M^+ + H).

Anal. Calcd. for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2\text{Se}$: C, 61.02; H, 5.36; N, 6.78. Found: C, 61.35; H, 5.32; N, 6.54.

6-[(3,5-Dimethylphenyl)selenenyl]-5-ethyl-1-(3-phenylpropyl)uracil (10d).

This compound was synthesized from **8b** with (3,5-dimethylphenyl)selenol in 98% yield, mp 142.3-143.4° (ethyl acetate); ir (potassium bromide): 1664, 1716 (CO) cm^{-1} ; ^1H nmr: δ 1.04 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.92 (tt, J = 8.0 Hz, J = 7.7 Hz, 2H, NCH_2CH_2), 2.26 (s, 6H, 2CH_3), 2.60 (t, J = 7.7 Hz, 2H, CH_2Ph), 2.75 (q, J = 7.4 Hz, 2H, CH_2CH_3), 4.04 (t, J = 8.0 Hz, 2H, NCH_2), 6.78 (s, 2H, Ar H), 6.89 (s, 1H, Ar H), 7.08-7.30 (m, 5H, Ar H), 8.49 (br s, 1H, NH); ms: m/z 442 (M^+ + H).

Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2\text{Se}$: C, 62.58; H, 5.94; N, 6.35. Found: C, 62.47; H, 5.99; N, 6.20.

1-Butyl-5-isopropyl-6-(phenylselenenyl)uracil (10e).

This compound was synthesized from **8c** with benzeneselenol in 98% yield, mp 104.3-105.0° (ethyl acetate-hexane); ir (potassium bromide): 1652, 1701 (CO) cm^{-1} ; ^1H nmr: δ 0.89 (t, J = 7.4 Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.19 (d, J = 6.9 Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.30 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.56 (m, 2H, NCH_2CH_2), 3.51 (septet, J = 6.9 Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 4.11 (t, J = 8.0 Hz, 2H, NCH_2), 7.25-7.40 (m, 5H, Ar H), 8.49 (br s, 1H, NH); ms: m/z 366 (M^+ + H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2\text{Se}$: C, 55.89; H, 6.07; N, 7.67. Found: C, 55.78; H, 6.23; N, 7.35.

1-Butyl-6-[(3,5-dimethylphenyl)selenenyl]-5-isopropyluracil (10f).

This compound was synthesized from **8c** with (3,5-dimethylphenyl)selenol in 99% yield, mp 132.3-133.1° (ethyl acetate-hexane); ir (potassium bromide): 1682, 1694 (CO) cm^{-1} ; ^1H nmr: δ 0.89 (t, J = 7.2 Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.21 (d, J = 6.9 Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.29 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.54 (m, 2H, NCH_2CH_2), 2.28 (s, 6H, 2CH_3), 3.52 (septet, J = 6.9 Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 4.11 (t, J = 8.0 Hz, 2H, NCH_2), 6.93 (m, 3H, Ar H), 8.52 (br s, 1H, NH); ms: m/z 394 (M^+ + H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_2\text{Se}$: C, 58.01; H, 6.66; N, 7.12. Found: C, 57.82; H, 6.76; N, 7.10.

5-Isopropyl-1-(3-phenylpropyl)-6-(phenylselenenyl)uracil (10g).

This compound was synthesized from **8d** with benzeneselenol in 99% yield, mp 112.4-112.8° (ethyl acetate-hexane); ir (potassium bromide): 1663, 1698 (CO) cm^{-1} ; ^1H nmr: δ 1.21 (d, J = 6.9 Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.94 (tt, J = 8.0 Hz, J = 7.5 Hz, 2H, NCH_2CH_2), 2.62 (t, J = 7.5 Hz, 2H, CH_2Ph), 3.51 (septet, J = 6.9 Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 4.11 (t, J = 8.0 Hz, 2H, NCH_2), 7.10-7.35 (m, 10H, Ar H), 8.47 (br s, 1H, NH); ms: m/z 428 (M^+ + 1).

Anal. Calcd. for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2\text{Se}$: C, 61.82; H, 5.66; N, 6.55. Found: C, 61.93; H, 5.45; N, 6.36.

6-[(3,5-Dimethylphenyl)selenenyl]-5-isopropyl-1-(3-phenylpropyl)uracil (10h).

This compound was synthesized from **8d** with (3,5-dimethylphenyl)selenol in 99% yield, mp 122.2-123.3° (ethyl acetate-hexane); ir (potassium bromide): 1668, 1698 (CO) cm^{-1} ; ^1H nmr: δ 1.22 (d, J = 6.9 Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.94 (tt, J = 8.0 Hz, J = 7.7 Hz, 2H, NCH_2CH_2), 2.26 (s, 6H, 2CH_3), 2.62 (t, J = 7.7 Hz, 2H, CH_2Ph), 3.51 (septet, J = 6.9 Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 4.12 (t, J = 8.0 Hz, 2H, NCH_2), 6.81 (s, 2H, Ar H), 6.89 (s, 1H, Ar H), 7.10-7.32 (m, 5H, Ar H), 8.40 (br s, 1H, NH); ms: m/z 456 (M^+ + H).

Anal. Calcd. for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_2\text{Se}$: C, 63.29; H, 6.20; N, 6.15. Found: C, 63.32; H, 6.25; N, 6.05.

1-Butyl-5-ethyl-6-(phenylselenenyl)-2-thiouracil (10i).

This compound was synthesized from **12a** with benzeneselenol in 76% yield, mp 122.5-124.0° (ethyl acetate); ir (potassium bromide): 1604 (CO) cm^{-1} ; ^1H nmr: δ 0.88 (t, J = 7.4 Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.14 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.30 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.51 (m, 2H, NCH_2CH_2), 2.86 (q, J = 7.4 Hz, 2H, CH_2CH_3), 3.32 (br s, 2H, NCH_2), 7.31-7.48 (m, 3H, Ar H), 7.58-7.66 (m, 2H, Ar H); ms: m/z 369 (M^+ + 2H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{OSSe}$: C, 52.31; H, 5.49; N, 7.63. Found: C, 52.23; H, 5.54; N, 7.48.

1-Butyl-6-[(3,5-dimethylphenyl)selenenyl]-5-ethyl-2-thiouracil (10j).

This compound was synthesized from **12a** with (3,5-dimethylphenyl)selenol in 74% yield, mp 125.7-127.4° (ethyl acetate-hexane); ir (potassium bromide): 1609 (CO) cm^{-1} ; ^1H nmr: δ 0.88 (t, J = 7.4 Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.14 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.32 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.52 (m, 2H, NCH_2CH_2), 2.33 (s, 6H, 2CH_3), 2.85 (q, J = 7.4 Hz, 2H, CH_2CH_3), 3.33 (br s, 2H, NCH_2), 7.05 (s, 1H, Ar H), 7.23 (s, 2H, Ar H); ms: m/z 397 (M^+ + 2H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{OSSe}$: C, 54.68; H, 6.12; N, 7.08. Found: C, 54.42; H, 6.35; N, 6.92.

5-Ethyl-1-(4-hydroxybutyl)-6-(phenylselenenyl)-2-thiouracil (**10k**).

This compound was synthesized from **12b** with benzeneselenol in 60% yield, mp 128.6-129.9° (ethyl acetate-hexane); ir (potassium bromide): 1586 (CO), 3447 (OH) cm^{-1} ; ^1H nmr: δ 1.12 (t, $J = 7.4$ Hz, 3H, CH_2CH_3), 1.57 (m, 2H, NCH_2CH_2), 1.67 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.84 (q, $J = 7.4$ Hz, 2H, CH_2CH_3), 3.34 (br s, 2H, NCH_2), 3.63 (t, $J = 5.9$ Hz, 2H, CH_2OH), 7.32-7.47 (m, 3H, Ar H), 7.57-7.66 (m, 2H, Ar H); ms: m/z 385 ($\text{M}^+ + 2\text{H}$).

Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2\text{SSe}$: C, 50.13; H, 5.26; N, 7.31. Found: C, 49.83; H, 5.48; N, 7.25.

6-[(3,5-Dimethylphenyl)selenenyl]-5-ethyl-1-(4-hydroxybutyl)-2-thiouracil (**10l**).

This compound was synthesized from **12b** with (3,5-dimethylphenyl)selenol in 64% yield, mp 139.0-139.5° (ethyl acetate); ir (potassium bromide): 1596 (CO), 3450 (OH) cm^{-1} ; ^1H nmr: δ 1.12 (t, $J = 7.4$ Hz, 3H, CH_2CH_3), 1.58 (m, 2H, NCH_2CH_2), 1.68 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.33 (s, 6H, 2CH_3), 2.83 (q, $J = 7.4$ Hz, 2H, CH_2CH_3), 3.37 (br s, 2H, NCH_2), 3.64 (t, $J = 5.9$ Hz, 2H, CH_2OH), 7.04 (s, 1H, Ar H), 7.22 (s, 2H, Ar H); ms: m/z 413 ($\text{M}^+ + 2\text{H}$).

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_2\text{SSe}$: C, 52.55; H, 5.88; N, 6.81. Found: C, 52.53; H, 5.95; N, 6.68.

1-Butyl-5-isopropyl-6-(phenylselenenyl)-2-thiouracil (**10m**).

This compound was synthesized from **12c** with benzeneselenol in 83% yield, mp 98.2-99.6° (ethyl acetate-hexane); ir (potassium bromide): 1601, 1622 (CO) cm^{-1} ; ^1H nmr: δ 0.87 (t, $J = 7.4$ Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.30 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.33 (d, $J = 6.9$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.51 (m, 2H, NCH_2CH_2), 3.29 (br s, 2H, NCH_2), 3.49 (septet, $J = 6.9$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 7.30-7.46 (m, 3H, Ar H), 7.54-7.66 (m, 2H, Ar H); ms: m/z 382 ($\text{M}^+ + \text{H}$).

Anal. Calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{OSSe}$: C, 53.54; H, 5.81; N, 7.35. Found: C, 53.62; H, 5.76; N, 7.22.

1-Butyl-6-[(3,5-dimethylphenyl)selenenyl]-5-isopropyl-2-thiouracil (**10n**).

This compound was synthesized from **12c** with (3,5-dimethylphenyl)selenol in 88% yield, mp 152.6-153.1° (acetonitrile); ir (potassium bromide): 1592, 1616 (CO) cm^{-1} ; ^1H nmr: δ 0.88 (t, $J = 7.4$ Hz, 3H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.30 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.34 (d, $J = 6.8$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.52 (m, 2H, NCH_2CH_2), 2.32 (s, 6H, 2CH_3), 3.32 (br s, 2H, NCH_2), 3.46 (septet, $J = 6.8$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 7.04 (s, 1H, Ar H), 7.22 (s, 2H, Ar H); ms: m/z 410 ($\text{M}^+ + \text{H}$).

Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{OSSe}$: C, 55.74; H, 6.40; N, 6.84. Found: C, 55.98; H, 6.36; N, 6.65.

1-(4-Hydroxybutyl)-5-isopropyl-6-(phenylselenenyl)-2-thiouracil (**10o**).

This compound was synthesized from **12d** with benzeneselenol in 69% yield, mp 149.8-150.3° (ethyl acetate); ir (potassium bromide): 1558, 1611 (CO), 3209 (OH) cm^{-1} ; ^1H nmr: δ 1.31 (d, $J = 6.8$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.55 (m, 2H, NCH_2CH_2), 1.66 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 3.34 (br s, 2H, NCH_2), 3.49 (septet, $J = 6.8$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 3.64 (t, $J = 5.9$ Hz, 2H, CH_2OH), 7.28-7.45 (m, 3H, Ar H), 7.57-7.63 (m, 2H, Ar H); ms: m/z 398 ($\text{M}^+ + \text{H}$).

Anal. Calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2\text{SSe}$: C, 51.38; H, 5.58; N, 7.05. Found: C, 51.22; H, 5.65; N, 6.98.

6-[(3,5-Dimethylphenyl)selenenyl]-1-(4-hydroxybutyl)-5-isopropyl-2-thiouracil (**10p**).

This compound was synthesized from **12d** with (3,5-dimethylphenyl)selenol in 62% yield, mp 162.8-163.4° (ethyl acetate); ir (potassium bromide): 1558, 1615 (CO), 3208 (OH) cm^{-1} ; ^1H nmr: δ 1.32 (d, $J = 6.9$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.57 (m, 2H, NCH_2CH_2), 1.68 (m, 2H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 2.32 (s, 6H, 2CH_3), 3.36 (br s, 2H, NCH_2), 3.48 (septet, $J = 6.9$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 3.65 (t, $J = 5.9$ Hz, 2H, CH_2OH), 7.03 (s, 1H, Ar H), 7.21 (s, 2H, Ar H); ms: m/z 426 ($\text{M}^+ + \text{H}$).

Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_2\text{SSe}$: C, 53.64; H, 6.16; N, 6.58. Found: C, 53.42; H, 6.21; N, 6.49.

Anti-HIV-1 Assay.

The anti-HIV-1 activity of compounds was evaluated on the basis of their inhibitory effect on virus-induced cytopathogenicity in MT-4 cells. The method described by Pauwels *et al.* [17] was used with a slight modification. Briefly, MT-4 cells were counted using a hemocytometer, diluted with culture medium, and plated in flat bottom, 96-well plates at a density of 1.0×10^4 cells in a volume of 50 μl . MT-4 cells were then either infected with HIV-1 (HTLV-III_B strain) of 500 TCID₅₀ (50% tissue culture infective dose) in a volume of 50 μl or mock-infected and were incubated for 1 hour at 37° in a highly humidified incubator containing 5% carbon dioxide. The test compounds were dissolved in dimethyl sulfoxide, diluted serially, and added to virus-infected wells in quadruplicate and mock-infected wells in duplicate in a volume of 100 μl to concurrently evaluate their effects on HIV- and mock-infected cells. After 5 days of incubation at 37° in an incubator containing 5% carbon dioxide, the viable cell number of each concentration was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method [18]. A 20 μl aliquot of MTT dissolved in phosphate-buffered saline (5 mg/ml) was added to each well, and the plates were incubated for an additional 4 hours. To solubilize formazan crystals, 100 μl of acidified 2-propanol was added to each well, and the plates were placed on a plate shaker for 20 minutes. The optical density (OD) was measured at 540 nm using an enzyme-linked immunosorbent assay (ELISA) reader (Dynatech, MR 5000, USA). Each experiment was repeated at least three times. The 50% cytotoxic concentration (CC₅₀) of test compounds which reduced OD of mock-infected control by 50% and the 50% effective concentration (EC₅₀) required to achieve the protection of cells against the cytopathogenicity of HIV-1 by 50% were calculated from dose-response curve plotted with probit analysis.

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- * To whom correspondence should be addressed.
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